

CRYSTALLINE FORMS OF HALOBETASOL PROPIONATE

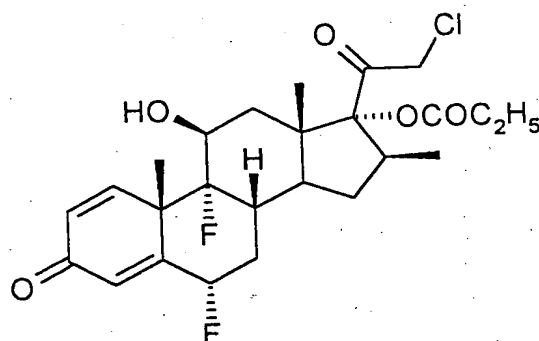
FIELD OF THE INVENTION

The present invention relates to new crystalline forms of halobetasol propionate, and processes for their preparation and stable topical pharmaceutical compositions based thereon.

The present specification is a continuation in part of USSN 10/341690 filed January 13, 2003 and entitled CRYSTALLINE FORMS OF HALOBETASOL PROPIONATE.

BACKGROUND OF THE INVENTION

The trihalogenated corticosteroid halobetasol propionate of the formula



also known as ulobetasol propionate is

(6 α ,9 α ,11 β ,16 β ,17 α)-21-Chloro-6,9-difluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)pregna-1,4-diene-3,20-dione.

Halobetasol propionate has been described in US patent No. 4,619,921 as a new topical polyhalogenated corticosteroid, presenting topical anti-inflammatory activity, whilst having low systemic activity. Halobetasol propionate is marketed in the U.S. as Ultravate[®] cream and Ultravate[®] ointment. It is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The search for new crystalline forms is relevant to the pharmaceutical sciences, since different crystalline forms of the same drug can possess different dissolution profile, pharmacokinetic profile and stability properties. The discovery of a new

crystalline form of a drug provides an opportunity to improve its performance - it broadens the repertoire of materials that a formulation scientist has available for designing, for example, a specific release profile.

The Ultravate products contain only one, yet uncharacterized, crystalline form. The efficacy and safety of other crystalline forms was heretofore unknown. The new crystalline forms are obtained economically, in very good yields via convenient processes and exhibit good stability. Most of the solvents used for their preparation (unlike those described in US 4,619,921) are safe and allow easy handling.

We have now surprisingly found that the new crystalline forms can be formulated in stable topical pharmaceutical compositions with similar or better efficacy than the marketed Ultravate® products.

In addition, the new crystalline forms exhibited excellent solubility and handling properties, allowing for a convenient pharmaceutical manufacturing process. They can be easily suspended or solubilized in the usual pharmaceutical ingredients.

Halobetasol propionate is described in the Merck Index and in US 4,619,921 as being crystallized from methylene chloride/ether and having a melting point of 220-221°C. The exact proportions of the two solvents were not given. Precise characterization of the above mentioned crystalline form of halobetasol propionate, using methods well known to those skilled in the art (powder X-ray diffraction, differential scanning calorimetry, infra-red spectroscopy, etc.) and the exact process for their preparation, is not given. There is no documented evidence that characterizes any crystalline form other than the melting point given in US 4,619,921.

The present invention provides six new crystalline forms of halobetasol propionate and processes for preparing them and stable topical pharmaceutical compositions containing the above crystalline forms.

SUMMARY OF THE INVENTION

The present invention provides new crystalline forms I-VI of halobetasol propionate, and processes for preparing them. Each of the new forms is differentiated by a unique powder X-ray diffraction pattern, and a unique infra-red spectrum.

The present invention also provides pharmaceutical compositions prepared from said halobetasol propionate. These formulations were found to be bioequivalent to presently marketed halobetasol propionate formulations.

A general technique that leads to the discovery of a novel crystalline form of a compound may be well known to those skilled in the art. Such techniques include crystallization, thermal treatment, and sublimation. Those skilled in the art appreciate that in the search for new polymorphic forms of a compound, any one of these techniques may fail to provide a new crystalline form of the compound. The search is an empirical exercise that involves trial and error experiments with different techniques and conditions. For these reasons, it is impossible to define all techniques and conditions that will produce halobetasol propionate Forms I-VI. It is, however, possible to provide methods which have successfully and selectively produced halobetasol propionate in one of these desired forms.

The novel crystalline forms of halobetasol propionate have been characterized by powder X-ray diffraction spectroscopy, which produces a fingerprint of the particular crystalline form. Measurements of 2θ values typically are accurate to within ± 0.2 degrees.

X-ray diffraction data were acquired using a PHILIPS X-ray diffractometer model PW1050-70. System description: $K\alpha_1=1.54178$, voltage 40kV, current 28 mA, diversion slit= 1° , receiving slit=0.2mm, scattering slit= 1° with a Graphite monochromator. Experiment parameters: pattern measured between $2\theta=4^\circ$ and $2\theta=30^\circ$ with 0.05° increments; count time was 0.5 second per increment.

The novel crystalline forms of halobetasol propionate have been further characterized by infra-red spectroscopy, which is directly related to the local environment around functional groups of a molecule. Different crystalline forms of the same compound can sometimes offer different environments around the molecule's functional groups, and/or different conformations of the molecule. These changes in local environment are mirrored in the Infra-red spectra of the various forms of halobetasol propionate.

Infra-red spectra were acquired using Nicolet Fourier-transform infra-red spectrometer model Avatar 360, with Omnic software version 5.2. All samples were run as Nujol[®] mulls. The current infra-red measurements are accurate to within 4 cm^{-1} .

Differential scanning calorimetry experiments were run on DuPont instruments model DSC 910, with software version 4.1C. Samples were analyzed inside 40 μl crimped Aluminum pan. Heating rate for all samples was 5°C/min. Since the melting of halobetasol propionate is accompanied by decomposition, the heating process was stopped slightly after the beginning of melting, in order to avoid damage to the measuring apparatus caused by decomposition products.

The novel forms of halobetasol propionate will now be described in more detail and with reference to the tables incorporated herein in which:

Table 1 represents powder X-ray diffraction peak positions and intensities of halobetasol propionate Form I.

Table 2 represents powder X-ray diffraction peak positions and intensities of halobetasol propionate Form II.

Table 3 represents powder X-ray diffraction peak positions and intensities of halobetasol propionate Form III.

Table 4 represents powder X-ray diffraction peak positions and intensities of halobetasol propionate Form IV.

Table 5 represents powder X-ray diffraction peak positions and intensities of halobetasol propionate Form V.

Table 6 represents powder X-ray diffraction peak positions and intensities of halobetasol propionate Form VI.

Halobetasol Propionate Form I

The present invention provides halobetasol propionate Form I. Form I produces a unique powder X-ray diffraction pattern (Table 1, Figure 1). The strong reflections at 11.6, 14.5, 18.1, 22.3, 23.0 \pm 0.2 degrees 2 θ are most characteristic of this form. Form I can be prepared by crystallization from methylene chloride:diethylether mixture (5:1), and can be separated conventionally from the solvent by filtering or decanting.

Table 1 – Form I
Powder X-ray diffraction peak positions and intensities

Relative Intensity (%)	Peak Position (2θ deg)	Relative Intensity (%)	Peak Position (2θ deg)
20.4	9.9	83.1	22.3
21.2	11.0	59.3	22.6
100.0	11.6	70.9	23.0
32.1	13.6	33.3	23.4
30.9	14.0	16.6	23.7
95.3	14.5	26.5	24.5
32.5	15.1	25.3	24.7
42.4	16.9	12.5	25.4
46.3	17.9	42.2	25.9
78.5	18.1	28.6	26.2
29.8	19.9	15.0	26.9
23.6	21.1	19.1	28.0
40.5	21.3	8.9	28.6
31.5	21.7	13.5	29.4

Form I is a solvate, containing around 9% (w/w) of methylene chloride. Weight loss around 90-100°C was detected by thermogravimetry analysis (TGA), and the

identity of the released solvent was independently determined using GC equipped with head-space accessory.

Apparently, this solvent loss is part of an irreversible solid-solid phase transition of Form I to Form III, accompanied by release of the methylene chloride. Upon heating to 90°C, this transition is completed after few minutes.

This transformation was observed visually using hot-stage microscopy, and it also appears as an endothermic peak in differential scanning calorimetry (DSC, Figure 13).

Form I produces a unique infra-red spectrum (Figure 7). The pattern created by the peaks at 1607, 1627, 1666, 1715, 1733 ± 4 cm⁻¹ is most characteristic of this form.

Surprisingly, halobetasol propionate Form I, obtained by crystallization from the same pair of solvents as the Form mentioned in US 4,619,921, although not necessarily in the same proportions. However, since the literature does not mention any transition and/or weight loss such as observed in Form I, these two Forms (our Form I and the form described in US 4,619,921) should be looked upon as two individual crystalline forms of halobetasol propionate.

Halobetasol Propionate Form II

The present invention provides halobetasol propionate Form II. Form II produces a unique powder X-ray diffraction pattern (Table 2, Figure 2). The strong reflections at 10.2, 13.0, 14.9, 16.1, 21.0 ± 0.2 degrees 2 θ are most characteristic of this Form. Form II may be prepared by crystallization from Toluene, and can be separated conventional from the solvent by filtering or decanting.

Table 2 – Form II
Powder X-ray diffraction peak positions and intensities

Relative Intensity (%)	Peak Position (2θ deg)	Relative Intensity (%)	Peak Position (2θ deg)
28.5	8.0	23.5	22.0
100	10.2	38.3	22.3
28.0	11.4	37.0	23.1
71.2	13.0	29.4	24.1
73.7	14.9	53.7	25.0
78.9	16.1	15.5	25.9
47.7	17.1	20.6	27.3
55.1	18.2	15.3	28.2
15.4	19.6	20.1	28.5
77.1	21.0	8.8	29.0

Form II can also be prepared by heating Form V to 90°C or heating Form VI to 175°C.

Melting range of Form II: 214.5-215.0°C with consequent decomposition.

DSC of Form II (Figure 14) showed only one endothermic peak that corresponds to its melting and consequent decomposition.

Form II has been heated at temperatures as high as 200°C without converting to another crystalline or amorphous form and without undergoing significant decomposition. Hot stage microscopy analysis of Form II showed no detectable transitions upon heating to its melting temperature.

Halobetasol propionate Form II produces a unique infra-red spectrum (Figure 8). The pattern created by the strong peaks at 1607, 1618, 1662 and 1723 \pm 4 cm⁻¹ is most characteristic of this form.

Halobetasol Propionate Form III

The present invention provides halobetasol propionate Form III. Form III produces a unique powder X-ray diffraction pattern (Table 3, Figure 3). The strong reflections at 13.0, 13.5, 14.6 and 23.6 ± 0.2 degrees 2θ are most characteristic of this form.

Table 3 – Form III
Powder X-ray diffraction peak positions and intensities

Relative Intensity (%)	Peak Position (2θ deg)	Relative Intensity (%)	Peak Position (2θ deg)
4.2	7.0	43.1	20.0
42.2	10.1	32.5	20.2
31.5	11.7	12.4	21.6
100.0	13.0	35.5	22.3
85.1	13.5	15.4	22.6
79.6	14.6	67.4	23.6
41.8	15.1	46.0	24.4
20.1	15.5	19.7	24.9
27.5	16.2	15.5	25.3
51.7	16.5	30.3	26.4
52.5	17.7	43.6	26.9
40.4	18.7	17.1	27.5
38.9	19.0	32.6	30.3

Form III may be prepared by crystallization from isopropanol, methylene chloride, or acetone, and it can be separated from the solvent conventionally by filtering or decanting.

Halobetasol propionate Form III can also be prepared by heating Form I to about 90°C or heating Form IV to 120°C .

Melting range of Form III: $205.8\text{--}209.0^\circ\text{C}$, with consequent decomposition.

Upon heating to 160°C , Form III undergoes a reversible solid-solid phase transition to an unknown form, without any weight loss. This transition was observed visually using hot-stage microscopy, and it also appears as an endothermic peak in DSC

(Figure 15). After cooling back to room temperature, the powder X-ray diffraction pattern of the heated material was identical to that of the starting material.

Form III has a unique infra-red spectrum (Figure 9). The pattern created by the strong peaks at 1611, 1627, 1665, 1708 and $1742 \pm 4 \text{ cm}^{-1}$ is particularly characteristic of this form.

Halobetasol Propionate Form IV

The present invention provides halobetasol propionate Form IV. Form IV produces a unique powder X-ray diffraction pattern (Table 4, Figure 4). The strong reflections at 9.4, 12.8, 13.1 and 19.1 ± 0.2 degrees 2θ are most characteristic of this form. Form IV may be prepared by crystallization from methanol:water (5:1) mixture, and can be separated conventionally from the solvent by filtering or decanting.

Table 4 – Form IV
Powder X-ray diffraction peak positions and intensities

Relative Intensity (%)	Peak Position (2θ deg)	Relative Intensity (%)	Peak Position (2θ deg)
9.7	6.7	21.5	20.7
60.9	9.4	26.8	20.9
32.1	11.5	59.2	21.5
81.5	12.8	19.2	22.8
100.0	13.1	13.6	23.6
48.5	13.6	40.5	24.0
49.0	13.8	25.3	24.4
22.7	14.5	19.8	24.7
32.2	14.8	2.4	25.2
55.5	15.1	8.8	25.6
43.1	15.4	39.2	26.4
13.2	17.4	12.3	26.7
43.1	18.3	34.7	27.2
39.1	18.6	32.6	28.2
66.2	19.1	35.4	28.7
25.5	19.7	19.7	28.9

The exact nature of Form IV is not completely clear. Samples dried at about 50°C showed the material to contain water and methanol. Weight loss of about 7-10 % (w/w) was detected by thermogravimetry (TGA). The identity of the released solvents was independently determined using GC equipped with head-space accessory and Karl Fischer titration.

Apparently, this solvent loss is part of an irreversible solid-solid phase transition of Form IV to Form III, accompanied by release of the solvents. Upon heating to about 120-130°C, this transition is completed after few minutes. This transition was observed visually by hot-stage microscopy, and it also appears as an endothermic peak in DSC (Figure 16). The same transition can be accomplished by heating Form IV under vacuum at about 60°C for about an hour or two.

Form IV has a unique infra-red spectrum (Figure 10). The patterns created by the strong peaks at 1606, 1621, 1664, 1711 and $1727 \pm 4 \text{ cm}^{-1}$, and three broad hydroxy absorption peaks at 3304, 3425 and $3580 \pm 4 \text{ cm}^{-1}$ are particularly characteristic of this form.

Halobetasol Propionate Form V

The present invention provides halobetasol propionate Form V. Form V crystallizes concomitantly with Form II by crystallization from ethyl acetate. The powder X-ray diffraction pattern of Form V can be differentiated by subtraction of the diffraction pattern of Form II from that of the mixture. Hence, Form V produces a unique powder X-ray diffraction pattern with reflections at 7.2, 8.5, 9.0, 9.5, 10.8, 14.0, 14.3, 15.3, 15.6, 16.2, 16.9, 17.7, 19.0, 20.1, 21.5, 22.9, 23.5, 23.6, 24.4, 25.4, 26.0, 26.9, 27.2, and 29.5 ± 0.2 degrees 2θ (Table 5, Figure 5).

Table 5 – Form V
Powder X-ray diffraction peak positions and intensities

Relative Intensity (%)	Peak Position (2θ deg)	Relative Intensity (%)	Peak Position (2θ deg)
39.5	7.2	100.0	19.0
3.8	8.5	18.3	20.1
16.9	9.0	52.8	21.5
72.1	9.5	30.0	22.9
6.3	10.8	26.0	23.5
85.1	14.0	20.2	23.6
62.6	14.3	27.8	24.4
49.4	15.3	14.0	25.4
95.0	15.6	30.5	26.0
34.5	16.2	12.3	26.9
38.1	16.9	14.2	27.2
12.7	17.7	23.9	29.5

Form V is a solvate, containing ethyl acetate. Weight loss of 4.4 % (w/w) around 90-100°C was detected by thermogravimetric analysis (TGA) of the mixture of the two forms. The identity of the released solvent was independently determined using GC equipped with head-space accessory.

Apparently, this solvent loss is part of an irreversible solid-solid phase transition of Form V to Form II, accompanied by release of the ethyl acetate. Upon heating to about 90°C, this transition is completed after few minutes. This transition was observed visually by hot-stage microscopy, and it also appears as an endothermic peak in DSC (Figure 17). Farther heating produced a plateau followed by melting and consequent decomposition at around 211-212°C.

The existence of Form V can also be identified by infra-red spectroscopy (Figure 11). The two peaks around $960 \pm 4 \text{ cm}^{-1}$ and the unique pattern around 1190 and $1300 \pm 4 \text{ cm}^{-1}$ can point to the presence of Form V.

Halobetasol Propionate Form VI

The present invention provides halobetasol propionate Form VI. Form VI produces a unique powder X-ray diffraction pattern (Table 6, Figure 6). The strong reflections at 9.7, 11.3, 12.6, 14.8, 15.7 ± 0.2 degrees 2 θ are particularly characteristic of this Form. Form VI can be prepared by crystallization from methanol and can be separated conventionally from the solvent by filtering or decanting.

Table 6 – Form VI
Powder X-ray diffraction peak positions and intensities

Relative Intensity (%)	Peak Position (2 θ deg)	Relative Intensity (%)	Peak Position (2 θ deg)
38.7	8.5	6.3	19.4
25.8	9.2	31.5	19.8
88.0	9.7	32.9	20.0
10.0	10.0	29.1	20.4
61.7	11.3	8.0	21.2
43.6	11.6	14.6	21.4
75.9	12.6	9.5	22.3
47.6	13.0	17.9	22.5
27.7	13.4	16.0	22.9
40.6	13.9	27.9	23.4
100.0	14.8	46.2	23.8
49.0	15.3	24.6	24.3
65.2	15.7	7.7	24.4
43.6	16.0	18.9	25.1
9.3	16.4	19.9	25.3
19.2	16.9	17.9	25.5
35.6	17.2	24.1	25.9
40.3	17.6	28.0	26.2
26.9	18.2	28.3	26.7
29.0	18.5	19.9	27.2

Upon heating to around 150-170°C, Form VI undergoes an irreversible solid-solid phase transition to Form II. DSC of Form VI (Figure 18) showed a shallow endothermic peak that started around 60°C, and ended at around 120°C. A second endothermic peak started at around 150°C, followed by an exothermic peak that started around 160°C and ended at around 180°C.

Analysis of Form VI by hot-stage microscopy showed a prolonged transition that started around 60°C and ended around 160-170°C.

Form VI produces a unique infra-red spectrum (Figure 12). The pattern created by the peaks at 1600, 1614, 1623, 1633, 1664, 1725 and $1735 \pm 4 \text{ cm}^{-1}$ and the occurrence of both free and associated hydroxyl peaks at 3659 and $3378 \pm 4 \text{ cm}^{-1}$ respectively, are most characteristic of this form.

The significance of the crystalline form of a corticosteroid is in the possible differences in their therapeutical activities. A different crystalline form of a corticosteroid may have a different physical properties. This might lead to different skin absorption and therefore to different clinical effect. In an article (Y. T. Sohn and S. Y. Kim "effect of crystal form on in vivo topical anti-inflammatory activity of corticosteroids" Archives of Pharmaceutical Research, Volume 24 No. 4, 556-559, 2002) the following is described: For each of the following corticosteroids (prednicarbate, betamethasone-17-valerate, hydrocortisone, prednisone and methyl prednisolone) two crystalline forms were prepared. The anti-inflammatory activity of their suspension in polyethylene glycol 400 was measured. In all the steroids, for each pair of crystalline forms, a significant difference in therapeutical activity was observed.

Halobetasol propionate ointment 0.05%, prepared according to example given in one of the embodiments of this patent application was compared to the commercial brand Ultravate® ointment. The comparison was made by comparing the blanching of the skin of human volunteers. This method called "vaso constricting assay" (VCA) was approved by the US FDA as a method of proving bioequivalence in topical corticosteroid compositions (FDA guideline "Topical Dermatological Corticosteroids; In Vivo Bioequivalence" June 1995). This study had shown that an ointment prepared by the present invention showed the same clinical activity as Ultravate® ointment.

While the invention will now be described in connection with certain preferred embodiments in the following examples and with reference to the attached figures so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

In the drawings:

Fig. 1 represents a powder X-ray diffraction pattern of halobetasol propionate Form I.

Fig. 2 represents a powder X-ray diffraction pattern of halobetasol propionate Form II.

Fig. 3 represents a powder X-ray diffraction pattern of halobetasol propionate Form III.

Fig. 4 represents a powder X-ray diffraction pattern of halobetasol propionate Form IV.

Fig. 5 represents a powder X-ray diffraction pattern of mixture of halobetasol propionate Form II and halobetasol propionate Form V.

Fig. 6 represents a powder X-ray diffraction pattern of halobetasol propionate Form VI.

Fig. 7 represents an infra-red spectrum of halobetasol propionate Form I.

Fig. 8 represents an infra-red spectrum of halobetasol propionate Form II.

Fig. 9 represents an infra-red spectrum of halobetasol propionate Form III.

Fig. 10 represents an infra-red spectrum of halobetasol propionate Form IV.

Fig. 11 represents an infra-red spectrum of mixture of halobetasol propionate Form II and halobetasol propionate Form V.

Fig. 12 represents an infra-red spectrum of halobetasol propionate Form VI.

Fig. 13 represents a differential scanning calorimetry curve of halobetasol propionate Form I.

Fig. 14 represents a differential scanning calorimetry curve of halobetasol propionate Form II.

Fig. 15 represents a differential scanning calorimetry curve of halobetasol propionate Form III.

Fig. 16 represents a differential scanning calorimetry curve of halobetasol propionate Form IV.

Fig. 17 represents a differential scanning calorimetry curve of mixture of halobetasol propionate Form II and halobetasol propionate Form V.

Fig. 18 represents a differential scanning calorimetry curve of halobetasol propionate Form VI.

EXAMPLES

EXAMPLE 1

(Preparation of halobetasol propionate Form I)

In a three necked round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 8 ml of boiling mixture of methylene chloride/diethylether (5:1). The solution was maintained at reflux during few minutes, and left at room temperature to cool down to 25°C. The resulting crystals (0.92 gr) were filtered and dried during one hour at 50°C in vacuum.

EXAMPLE 2

(Preparation of halobetasol propionate Form II)

In a three necked round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 8 ml of boiling toluene. The solution was maintained at reflux during few minutes, and left at room temperature to cool down to 25°C. The resulting crystals (0.95 gr) were filtered and dried during one hour at 50°C in vacuum.

EXAMPLE 3

(Preparation of halobetasol propionate Form II)

In a three necked round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 8 ml of boiling toluene. The solution was maintained at reflux during few minutes, and left inside hot mineral oil for slow cooling, until the oil cooled down to 25°C. The resulting crystals (0.95 gr) were filtered and dried during one hour at 50°C in vacuum.

EXAMPLE 4

(Preparation of halobetasol propionate Form II)

In a 20 ml scintillation vial, halobetasol propionate Form V (1 gr) was heated to 120°C during 10 minutes.

EXAMPLE 5

(Preparation of halobetasol propionate Form II)

In a 20 ml scintillation vial, halobetasol propionate Form VI (1 gr) was heated to 180°C during 10 minutes.

EXAMPLE 6

(Preparation of halobetasol propionate Form III)

In a three necked round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 3 ml of boiling isopropanol. The solution was maintained at reflux during few minutes, and left to cool down to 25°C. Alternatively, the solution was cooled to 0°C by dipping the flask in ice. The resulting crystals (0.90 gr) were filtered and dried one hour at 50°C in vacuum.

EXAMPLE 7

(Preparation of halobetasol propionate Form III)

In a three necked round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 1 ml of boiling acetone. The solution was maintained at reflux during few minutes, and left to cool to 25°C. The resulting crystals (0.95 gr) were filtered and dried one hour at 50°C in vacuum.

EXAMPLE 8

(Preparation of halobetasol propionate Form III)

In a three neck round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 10 ml of boiling methylene chloride. The solution was maintained at reflux during few minutes, and then evaporated using a rotary evaporator. The resulting solid was dried in high vacuum at room temperature.

EXAMPLE 9

(Preparation of halobetasol propionate Form III)

In a 20 ml scintillation vial, halobetasol propionate Form I (1 gr) was heated to 140°C during 10 minutes.

EXAMPLE 10

(Preparation of halobetasol propionate Form III)

In a 20 ml scintillation vial, halobetasol propionate Form IV (1 gr) was heated to 120°C during 10 minutes.

EXAMPLE 11

(Preparation of halobetasol propionate Form IV)

In a three neck round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 10 ml of boiling methanol. The solution was maintained at reflux during few minutes, and then 2 ml of water was added dropwise. The solution was cooled slowly to room temperature during 3 hours. The resulting crystals (0.7-0.8 gr) were dried during one hour at 50°C in vacuum.

EXAMPLE 12

(Preparation of halobetasol propionate Form V)

In a three necked round bottom flask equipped with a reflux condenser, a thermometer and a magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 3 ml of boiling ethyl acetate. The solution was maintained at reflux during few minutes, and left to cool to 25°C. The resulting crystals (0.85 gr) were filtered and dried during one hour at 50°C in vacuum.

EXAMPLE 13

(Preparation of halobetasol propionate Form VI)

In a three necked round bottom flask equipped with a reflux condenser, a thermometer and an magnetic stirrer, halobetasol propionate (1 gr) was dissolved in 10 ml of boiling methanol. The solution was maintained at reflux during few minutes, and left to cool to 25°C. The resulting crystals (0.85 gr) were filtered and dried during one hour at 50°C in vacuum.

EXAMPLE 14

(Preparation of halobetasol propionate ointment 0.05%)

Ingredients:

Halobetasol propionate	0.05%
White petrolatum USP	79.95%
Dehymuls E	7.5%
White wax NF	5%
Propylene glycol USP	7.5%

Procedure:

Component A: Heat to 70°C and mix together white petrolatum NF, Dehymuls E and white wax NF.

Component B: Heat propylene glycol USP to 70°C and add with high shear mixing halobetasol propionate to dissolution.

Using a high shear mixer add, under vacuum, component B to component A. Cool the product.

EXAMPLE 15

(Preparation of halobetasol propionate cream 0.05%)

Ingredients:

Halobetasol propionate	0.05%
Cetyl alcohol NF	6%

Isopropyl isostearate	3%
Isopropyl palmitate NF	2%
Steareth 21	3%
Germall II	0.2%
Glycerin 99.5% USP	2%
Kathon CG	0.05%
Purified water (part A)	78.7%
Purified water (part B)	5%

Procedure:

Component A: Heat to 70°C and mix cetyl alcohol NF, isopropyl isostearate, isopropyl palmitate NF and Steareth 21.

Component B: Heat to 70°C and mix purified water (part A) and Germall II.

Component C: With high shear mixing mix glycerin, Kathon CG and halobetasol propionate. Then add gradually purified water (part B).

Using a high shear mixer mix component A to component B. Adjust temperature to 40°C.

Add the component C, using a high shear mixer, to the combined components A and B. Cool.

EXAMPLE 16

(Preparation of halobetasol propionate emollient ointment 0.05%)

Ingredients:

Halobetasol propionate	0.05%
Softisan 378	71.95%
Propylene glycol monostearate	8%
Castor oil	15%
Oleyl alcohol	5%

Procedure:

Heat together oleyl alcohol and castor oil to 60°C. Add halobetasol propionate . Mix to dissolution.

Separately heat Softisan 378 and propylene glycol monostearate to 55-60°C.

Add, under vacuum the second solution to the first. Cool.

EXAMPLE 17

(VCA bioequivalence study of halobetasol propionate ointment 0.05%)

An ointment formulation prepared from halobetasol propionate having crystalline form III was prepared according to example 14. An *In Vivo* study compared the vaso-constricting activity (VCA) of this cream and Ultravate® ointment 0.05%. The VCA study was done according to the US FDA guideline "Topical Dermatological Corticosteroids: In Vivo Bioequivalence" June 2, 1995). The result of the study showed the bioequivalence of both compositions.

	N	Means		Ratio (%)	90% confidence interval	
		Test	Reference		Lower (%)	Higher (%)
Chromameter reading	35	13.5	13.0	103.8	91.2	118.6

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.